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# Accepted Manuscript

Exercise guidelines to promote cardiometabolic health in spinal cord injured humans: time to raise the intensity?

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2

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5

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**Abstract**

Spinal cord injury (SCI) is a life changing event that, as a result of paralysis, negatively influences habitual levels of physical activity and hence cardiometabolic health. Performing regular structured exercise therefore appears extremely important in persons with SCI. However, exercise options are mainly limited to the upper-body, which involves a smaller activated muscle mass compared to the mainly leg-based activities commonly performed by non-disabled individuals. Current exercise guidelines for SCI focus predominantly on relative short durations of moderate-intensity aerobic arm cranking exercise, yet contemporary evidence suggests this is not sufficient to induce meaningful improvements in risk factors for the prevention of cardiometabolic disease in this population. As such, these guidelines and their physiological basis, require reappraisal. In this special communication, we propose that high-intensity interval training (HIIT) may be a viable alternative exercise strategy, to promote vigorous-intensity exercise and prevent cardiometabolic disease in persons with SCI. Supplementing the limited data from SCI cohorts with consistent findings from studies in non-disabled populations, we present strong evidence to suggest that HIIT is superior to moderate-intensity aerobic exercise for improving cardiorespiratory fitness, insulin sensitivity and vascular function. The potential application and safety of HIIT in this population is also discussed. We conclude that increasing exercise intensity could offer a simple, readily available, time-efficient solution to improve cardiometabolic health in persons with SCI. We call for high-quality randomised controlled trials to examine the efficacy and safety of HIIT in this population.

**Key words:** Spinal cord injury, Cardiometabolic health, High-intensity interval training, Vigorous-intensity exercise, Cardiorespiratory fitness

**Abbreviations:**

CVD- cardiovascular disease,

FMD- flow-mediated dilation,

HbA1c- glycated haemoglobin,

HDL-C- high-density lipoprotein cholesterol

HIIT- high-intensity interval training,

HRmax- maximum heart rate,

LDL-C- low-density lipoprotein cholesterol

MICT- moderate-intensity continuous training,

OGTT- oral glucose tolerance test,

PAG-SCI- physical activity guidelines for people with a spinal cord injury,

RPE- rating of perceived exertion,

SCI- spinal cord injury,

SIT- sprint interval training,

T2DM- type-2 diabetes mellitus,

$\dot{V}O_{2peak}$  - maximal oxygen uptake.

## 76 1 Introduction

77

78 Spinal cord injury (SCI) creates a complex pathophysiology, characterised by paralysis,  
79 which has wide-ranging implications for multiple body systems. For persons with SCI,  
80 chronic cardiometabolic diseases occur at a heightened frequency and earlier in the  
81 lifespan compared to non-disabled individuals <sup>1-3</sup>. Given that more than 2 million people  
82 currently live with SCI worldwide and the incidence of SCI is highest among young  
83 adults <sup>4</sup>, it is clear that there is an increased and prolonged demand on medical and  
84 support resources for persons aging with paralysis. Despite the known, undisputed  
85 health benefits of physical activity in non-disabled individuals <sup>5-7</sup>, research suggests  
86 patients with SCI perform little to no physical activity <sup>8-11</sup>, and this is likely a key driver  
87 of the greater prevalence of cardiometabolic disease in this population <sup>12, 13</sup>. Therefore,  
88 it is a priority to develop evidence-based, effective physical activity recommendations  
89 for the prevention of chronic disease in persons with SCI.

90

91 The recently re-published Physical Activity Guidelines for Spinal Cord Injury (PAG-  
92 SCI) recommends at least 20 minutes of moderate to vigorous-intensity aerobic exercise  
93 twice a week (40 min/wk) <sup>14</sup>, while a recent position statement from Exercise and Sports  
94 Science Australia recommends  $\geq 150$  min/wk of moderate-intensity or  $\geq 60$  min/wk of  
95 vigorous-intensity exercise <sup>15</sup>. Both of these guidelines also include strength training  $\geq 2$   
96 day/wk <sup>14, 15</sup>. Regardless of the large discrepancy between these guidelines in terms of  
97 the recommended volume of moderate-intensity exercise, they remain indifferent from  
98 the *minimum* amount of exercise which is promoted by reputable, international health  
99 authorities [Centers for Disease Control (CDC) and World Health Organisation (WHO)]  
100 in order to reduce the risk of developing cardiometabolic disease in the general

101 population. However, it is noteworthy that the exercise guidelines for non-disabled  
102 populations are based on lower-body or whole-body activity (e.g. walking, running,  
103 cycling), whereas exercise for persons with SCI is primarily restricted to the smaller  
104 upper-body skeletal muscles [e.g. arm-crank exercise or wheelchair propulsion]. As a  
105 result of the smaller active muscle mass and blunted haemodynamic responses with  
106 SCI, the absolute capacity for physical exercise is reduced<sup>16-18</sup>. Therefore, at the same  
107 relative intensity, the absolute energy expenditure, cardiovascular strain, and whole-  
108 body metabolic demand, will always be lower during moderate-intensity arm-crank  
109 exercise or wheelchair propulsion compared with moderate-intensity walking or  
110 cycling. The ability for skeletal muscle to adapt to the same stimulus will not be  
111 reduced; however, the smaller active muscle mass means that modest training-induced  
112 adaptations in the arm are less likely to impact biomarkers of cardiometabolic health. As  
113 such, to promote a *lower* volume of exercise in this population would seem  
114 physiologically counterintuitive, whilst promoting a *similar* volume of exercise would  
115 likely be less effective. In accordance with this, a recent randomised controlled trial  
116 demonstrated that performing PAG-SCI for 16 weeks was insufficient to promote  
117 clinically meaningful changes in both novel and traditional biomarkers of  
118 cardiovascular disease (CVD)<sup>19</sup>. Moreover, a systematic review requested by the  
119 Consortium for Spinal Cord Medicine<sup>20</sup> concluded that the current evidence is  
120 insufficient to determine whether these volumes of exercise are associated with positive  
121 changes in carbohydrate and lipid metabolism (and associated disorders) amongst adults  
122 with SCI. Therefore, we contend that these guidelines, and their physiological  
123 justification, require reappraisal, and that there is need to develop more effective,  
124 alternative approaches.

125



126 There are numerous psychosocial and environmental barriers to engage in physical  
127 activity for individuals that use wheelchairs<sup>21-24</sup>. Moreover, compromised venous  
128 return in persons with SCI blunts cardiac output<sup>25</sup>, which can lead to an early onset of  
129 muscle fatigue<sup>26</sup>, thus reducing ones capacity for prolonged exercise. Therefore,  
130 promoting a *larger* volume of moderate-intensity exercise might not be feasible in this  
131 population. Functional electronic stimulation<sup>27-30</sup> and body weight supported treadmill  
132 training<sup>31</sup>, have received considerable research attention, but have numerous practical  
133 limitations (i.e. significant cost and specialist resources required), and may have limited  
134 application outside the laboratory. One potential alternative approach, which has  
135 received less attention, would be to recommend high-intensity interval training (HIIT)  
136 as a practical means of increasing vigorous-intensity exercise. The benefit of vigorous-  
137 intensity physical activity is supported by a number of epidemiological studies, albeit in  
138 non-disabled individuals, demonstrating superior reductions in the risk of  
139 cardiovascular<sup>32, 33</sup> and all-cause mortality<sup>34-36</sup>, in comparison to light-to-moderate  
140 intensity physical activity. Moreover, accumulating evidence, from studies applying  
141 HIIT in non-disabled populations, demonstrates that HIIT promotes superior peripheral  
142<sup>37</sup> and whole-body adaptations<sup>38-40</sup>, compared with moderate-intensity continuous  
143 training (MICT). HIIT may therefore offer a simple, more effective alternative to  
144 current approaches for improving cardiometabolic health in persons with SCI. In the  
145 following sections we put forward the case for recommending HIIT in SCI, and  
146 subsequently consider its potential practical application and safety in this population.

147

148

149

## 2 High-intensity Interval Training to Facilitate Vigorous-intensity Exercise in Spinal Cord Injury

HIIT encompasses exercise performed above the intensity which elicits the maximal lactate steady state. Any exercise above this threshold results in the progressive accumulation of intramuscular and systemic metabolites that are implicated in fatigue. As such, exercise intensities above this threshold ( $\sim 80\text{-}85\%$   $\dot{V}O_{2\text{peak}}$ ) cannot be maintained for a prolonged period of time. The exercise must therefore be performed in intervals interspersed with periods of low-intensity or resting recovery. The main justification for HIIT is that it allows a greater volume of vigorous-intensity exercise to be accrued in a single exercise session, and accumulating evidence suggests that this can be of great physiological and clinical benefit<sup>38-40</sup>.

A wide range of HIIT protocols have been utilised in the literature but with limited standardisation of the terminology used to classify different protocols. Furthermore, studies have prescribed exercise intensities as a percentage of different maximal physiological responses [e.g. maximum heart rate ( $HR_{\text{max}}$ )<sup>41</sup>, heart rate reserve<sup>42</sup>, age-predicted max heart rate<sup>43</sup> and peak oxygen uptake ( $\dot{V}O_{2\text{peak}}$ )<sup>44</sup>] and, for these reasons, may not be directly comparable, particularly in individuals with low baseline fitness<sup>45</sup>. Nevertheless, for the purposes of this review, we adopt the terminology proposed by Weston *et al.*<sup>38</sup>, whereby HIIT describes protocols using intensities between 80-100% of  $HR_{\text{max}}$ , whereas protocols using ‘all-out’ efforts, or efforts  $\geq 100\%$   $\dot{V}O_{2\text{peak}}$ , are referred to as sprint interval training (SIT) (Figure 1). There is good evidence that both HIIT and SIT provide equal or even superior physiological adaptations compared with MICT<sup>46-50</sup>. However, as SIT protocols may be more difficult to adapt in order to

provide a practical intervention for persons with SCI, in this review we draw mainly on HIIT studies to support the argument for vigorous-intensity exercise. Example HIIT protocols tested in both the SCI and non-disabled literature are described in Table 1.

[INSERT FIGURE 1 ABOUT HERE]

[INSERT TABLE 1 ABOUT HERE]

### 3 Moderate vs Vigorous-intensity Exercise for Cardiometabolic Health

#### 3.1 Cardiorespiratory Fitness and Skeletal Muscle Oxidative Capacity

Poor cardiorespiratory fitness has been widely reported in individuals with SCI<sup>52, 53</sup>. Although just ~90 min/wk<sup>44, 54</sup> of MICT is sufficient to promote modest improvements (~10%) in  $\dot{V}O_{2peak}$ , a substantially larger volume (180 min/wk) is necessary for greater improvements (~19%)<sup>55</sup>. Vigorous-intensity exercise offers superior benefits and is more time efficient. Of the two studies which have used time-matched training protocols in SCI (Table 2) there are negligible (12% vs. 10%)<sup>42</sup> and considerable (50% vs. 17%)<sup>56</sup> improvements in  $\dot{V}O_{2peak}$  with vigorous-intensity compared to moderate-intensity exercise, respectively. The larger improvement in the De Groot *et al.*<sup>56</sup> study could be due to participants having acute (< 225 days) injuries or the greater volume of accumulated vigorous-intensity activity (additional 48 min/wk). More recently, unpublished data from Sæter<sup>57</sup>, which adopted a more robust isocaloric study design, demonstrated a superior stimulus for  $\dot{V}O_{2peak}$  and PPO with vigorous-intensity exercise

200 compared to MICT. Furthermore, a case-study demonstrated a 52% increase in  $\dot{V}O_{2peak}$   
 201 in a 42 year old man with SCI following just 6 weeks of HIIT<sup>58</sup>.  
 202  
 203 Several studies have directly compared the effects of energy-matched HIIT and MICT  
 204 on  $\dot{V}O_{2peak}$  in deconditioned (non-disabled) individuals with pre-existing  
 205 cardiometabolic disease and these have clearly demonstrated that HIIT results in  
 206 superior improvements. These studies were summarised in a recent meta-analysis  
 207 which, using data from 10 studies and 273 participants, showed that the increase in  
 208  $\dot{V}O_{2peak}$  following HIIT was approximately twice (~3 ml/kg/min) that observed  
 209 following MICT<sup>38</sup>. This finding has been reproduced in various non-disabled  
 210 populations including healthy young and middle-aged sedentary men<sup>59,60</sup>, overweight  
 211 and obese men and women<sup>61</sup>, and in individuals with type-2 diabetes mellitus (T2DM)  
 212<sup>62</sup>. A 3 ml/kg/min improvement in cardiorespiratory fitness is associated with a 15% and  
 213 19% reduction in all-cause and CVD mortality, respectively, and is on par with a 7 cm  
 214 reduction in waist circumference, a 5 mmHg reduction in systolic blood pressure, or a 1  
 215 mmol/L drop in fasting plasma glucose<sup>63,64</sup>. Given that cardiorespiratory fitness  
 216 consistently manifests as the strongest predictor of cardiometabolic disease risk and  
 217 longevity in epidemiological studies<sup>65-68</sup>, these findings are an important point of  
 218 reference in the argument for applying HIIT, as a model to increase vigorous-intensity  
 219 physical activity, in individuals with SCI.  
 220  
 221 Although still a subject of debate<sup>69-71</sup>, recent evidence supports, at least partially, the  
 222 role of peripheral muscle characteristics, in particular absolute mitochondrial capacity  
 223 (i.e. maximal mitochondrial oxygen utilization), in limiting  $\dot{V}O_{2peak}$ , and hence  
 224 underpinning changes in  $\dot{V}O_{2peak}$  with exercise training<sup>72,73</sup>. It is noteworthy then that a

recent study convincingly demonstrated that cycling based HIIT induced superior mitochondrial adaptations compared with MICT, in muscle taken from the lower limb<sup>37</sup>. Arm exercise training may not be sufficient to induce central hemodynamic adaptations<sup>74</sup>, but can be expected to induce peripheral mitochondrial adaptations. Thus, if the superior effects observed with HIIT compared with moderate-intensity cycling and walking/running in non-disabled individuals are translatable to arm exercise training in persons with SCI, then HIIT may provide a more effective intervention for improving  $\dot{V}O_{2peak}$  in persons with SCI. Moreover, the superior changes in mitochondrial oxidative capacity with HIIT may have implications for other cardiometabolic risk factors such as insulin sensitivity and glycaemic control<sup>75</sup>.

*[INSERT TABLE 2 ABOUT HERE]*

### **3.2 Insulin Action and Glycaemic Control**

Insulin resistance is a pre-requisite to T2DM. It is characterised by the failure of insulin to exert the normal cellular effects on various tissues, leading to the impairment of insulin mediated glucose disposal. Fasting hyperglycaemia can persist due to the insensitivity of the liver to the suppressive effects of insulin on gluconeogenesis and reduced glycogenolysis<sup>76</sup>. Consequently fasting plasma glucose concentrations have been shown to correlate with basal rates of hepatic glucose output<sup>77</sup>. Therefore, as fasting plasma glucose concentrations tend to be only mildly elevated in individuals with SCI<sup>78</sup>, it is most likely that peripheral insulin resistance is the major driver behind impaired glycaemic control in this population. The lack of stimulation and disuse because of paralysis can have a profound impact on skeletal muscle below the level of

injury, including i) atrophy of lean mass<sup>79-82</sup>, which diminishes the tissue available for glucose disposal (Figure 2a)<sup>83, 84</sup>, and ii) accumulation of intramuscular fat<sup>85, 86</sup>.

[INSERT FIGURE 2 ABOUT HERE]

Recent publications have demonstrated that moderate-intensity arm-crank ergometry improves insulin resistance, as determined by HOMA-IR<sup>87, 88</sup>. Although this is promising, HOMA-IR reflects hepatic insulin sensitivity, whereas indices derived during postprandial oral glucose tolerance tests (OGTT), such as the ISI<sub>matsuda</sub>, represent predominantly peripheral insulin sensitivity<sup>89, 90</sup>. Data from the HOMEX-SCI trial, including both fasting and provocative dynamic testing, would suggest arm-crank MICT (60 – 65%  $\dot{V}O_{2peak}$ , 180 min/wk) in persons with chronic paraplegia improves hepatic but not whole-body insulin sensitivity<sup>55</sup>. Therefore, moderate-intensity arm-crank exercise might not be sufficient to overcome insulin resistance in peripheral tissues. There is a paucity of research comparing both fasting and dynamic glucose and insulin responses to HIIT or MICT in the context of arm-crank exercise in the SCI population. Insulin sensitivity data from De Groot *et al*<sup>56</sup> is counter-intuitive, in that it demonstrates non-significant improvements in the moderate-intensity group and reduced insulin sensitivity in the high-intensity group. This may be explained by a natural regression to the mean effect (i.e. greater proportion of insulin resistant individuals in the low-intensity group at baseline). These results should be viewed with caution due to the, (i) small sample size (n=3 per group) and, (ii) the marked age and sex differences between the two groups, which could impact exercise responses.

275 The impact of HIIT on insulin action and glycaemic control in non-disabled populations  
 276 has recently been summarised by Jelleyman *et al*,<sup>40</sup> in a meta-analysis of 50 training  
 277 studies. Their analyses demonstrated that HIIT was associated with improved insulin  
 278 sensitivity (estimated via fasting or OGTT-derived indices) and reduced fasting glucose  
 279 when compared to both baseline and/or changes in a no-exercise control group<sup>40</sup>. The  
 280 magnitude of change appeared to be greater in populations with insulin resistance (e.g.  
 281 T2DM or metabolic syndrome) with reductions in glycated haemoglobin (HbA1c) also  
 282 observed in this group<sup>40</sup>. When compared with MICT there appeared to be greater  
 283 improvements in markers of insulin sensitivity with HIIT (both fasting and dynamic  
 284 combined), but no difference in the change in fasting glucose, insulin or HbA1c in  
 285 isolation<sup>40</sup>. These differences were apparent despite the fact that the methods varied  
 286 considerably between studies. This included variations in the HIIT protocols utilised  
 287 (e.g. SIT vs HIIT, cycling vs running), the techniques used to assess insulin sensitivity  
 288 (e.g. fasting vs OGTT vs clamp) and the duration after the final training session in  
 289 which the insulin sensitivity data was captured. Moreover, studies had been performed  
 290 in a wide variety of populations. As such, there is sufficient evidence that in non-  
 291 disabled populations with insulin resistance HIIT is associated with superior changes in  
 292 markers of insulin sensitivity compared to MICT<sup>62, 91-95</sup>.

293  
 294 It is also important to consider the acute effects of MICT and HIIT on glycaemic  
 295 control, although this has received less research attention, especially in SCI individuals.  
 296 Two studies have examined the acute effects of HIIT vs MICT on glycaemic control,  
 297 using continuous glucose monitors to capture 24-hour glucose profiles, and have shown  
 298 superior effects with HIIT in both obese men<sup>96</sup> and individuals with T2DM<sup>97</sup>. These  
 299 effects are underpinned by a plausible mechanism given that high-intensity exercise is

300 associated with greater muscle glycogen utilisation<sup>98</sup> and muscle glycogen  
 301 concentrations are an important driver of acute changes in insulin sensitivity with  
 302 exercise<sup>99-101</sup>. Clearly, the acute effects of exercise, as well as comparisons of HIIT and  
 303 MICT, on glycaemic control in SCI individuals, is an important area of future research.

304

305

### 306 **3.3 Vascular Function and Blood Pressure**

307

308 Arterial stiffness<sup>102</sup> and endothelial function<sup>103, 104</sup> are important predictors of future  
 309 cardiovascular health. Individuals with SCI are characterised by severe deterioration of  
 310 structure and function of vessels below the level of injury<sup>105</sup>, but evidence also suggests  
 311 increased stiffness and impaired endothelial function within central and regional upper  
 312 body arteries in SCI relative to non-disabled controls<sup>106</sup>. Recent evidence suggests that  
 313 achieving the PAG-SCI for 16-weeks is insufficient to improve the health of both lower  
 314 and upper-limb, as well as central blood vessels<sup>19</sup>.

315

316 A recent meta-analysis, including 182 participants from 7 studies, demonstrated that  
 317 HIIT was superior to MICT for improving markers of endothelial function<sup>39</sup>. Within  
 318 the meta-analysis, studies that had utilised a work-matched HIIT protocol, consisting of  
 319 4 x 4 min at 85-90% HR<sub>max</sub>, appeared to show the most consistent benefit of HIIT over  
 320 and above improvements observed with MICT<sup>61, 91, 107, 108</sup>. A 1% increase in FMD  
 321 (flow-mediated dilation) is associated with a 13% reduction in the risk of cardiovascular  
 322 events<sup>103</sup>. Therefore the 2.6% magnitude of difference in the change in FMD observed  
 323 between HIIT and MICT in this meta-analysis would be expected to result in clinically  
 324 meaningful risk reduction<sup>39</sup>.



325 Individuals with lower-level spinal cord lesions experience similar hypertension issues  
 326 as the general population <sup>109</sup>, whereas individuals with higher-level lesions ( $\geq$  T6) often  
 327 suffer from hypotension <sup>110</sup>. A direct comparison of moderate and high-intensity  
 328 exercise training on blood pressure is not available in SCI. However, in non-disabled  
 329 individuals, evidence suggests that several months of HIIT or MICT are able to induce  
 330 comparable changes in both systolic and diastolic blood pressure in a variety of  
 331 populations <sup>60, 61, 91, 111</sup>.

### 334 3.4 Body Composition

336 Individuals with SCI demonstrate a greater propensity to accumulate excess body fat  
 337 compared to non-disabled populations <sup>112, 113</sup>. Furthermore, due to the accelerated loss  
 338 of lean mass, the distribution of adipose tissue in SCI also appears to be altered <sup>114</sup>,  
 339 which would be expected to exert detrimental metabolic effects <sup>115-118</sup>. It is therefore  
 340 important to consider the role physical activity plays in maintaining body composition  
 341 and the potential contribution towards a sustained energy deficit to reduce adiposity.  
 342 Yet, large additions to weekly total energy expenditure (TEE) through structured  
 343 exercise (i.e. on top of baseline physical activity) are required to induce meaningful  
 344 reductions in body fat <sup>119</sup>. For example, Donnelly *et al.*, <sup>120</sup> suggested that a meaningful  
 345 body mass reduction requires an exercise energy expenditure in excess of 2000 kcal/wk.  
 346 If we extrapolate from exercise data for inactive SCI participants in the HOMEX-SCI  
 347 trial <sup>55</sup>, achieving this would require approximately 448 min/wk of moderate-intensity  
 348 arm-crank exercise. Therefore, it is perhaps not surprising that following PAG-SCI for

16 weeks does not induce significant reductions in total and visceral fat mass, although it may be sufficient to reduce the rate of increase in adiposity<sup>19</sup>.

351

There is good evidence from non-disabled studies that HIIT can be an effective intervention for promoting positive changes in body composition, including reductions in total body mass<sup>59, 91, 121-123</sup>, total fat percentage<sup>122-125</sup>, total abdominal fat mass<sup>91, 122-124</sup> and waist circumference<sup>91, 122, 126</sup>. However, perhaps as expected, studies that have compared energy-matched HIIT and MICT interventions (i.e. both interventions would increase TEE to a similar extent) over several months have demonstrated comparable changes in body composition<sup>61, 91, 121</sup>. Interestingly, it also appears that HIIT protocols requiring lower exercise volumes (e.g. low-volume HIT or SIT) are associated with similar increases in total 24-hour energy expenditure to 30-50 min of MICT<sup>127, 128</sup> and can also induce meaningful reductions in total and abdominal fat<sup>124, 129</sup>, which are comparable to 30-45 min of MICT in overweight/obese individuals<sup>123</sup>. Increases in leg lean mass have also been observed with cycling based HIIT<sup>122, 124</sup>, and this has the potential to also translate to the upper-body musculature in patients with SCI. While HIIT does not appear to induce a greater reduction in adiposity than MICT, the reviewed evidence would suggest it is equally as effective, but with a reduction in exercise time commitment.

368

369

### 3.5 Fasting and Postprandial Dyslipidaemia

371

A recent meta-analysis<sup>130</sup> highlighted that persons with SCI have a unique lipid profile, primarily characterised by depressed high-density lipoprotein cholesterol (HDL-C). Hooker & Wells<sup>42</sup> showed a trend for increased (21%) HDL-C and reduced (-15%)

low-density lipoprotein cholesterol (LDL-C) with vigorous but not moderate-intensity exercise over 8 weeks. Other trials specifically in persons with SCI demonstrated no impact of exercise-intensity on lipid profiles. Greater or similar improvements in HDL-C with HIIT compared to MICT have been shown in populations with cardiometabolic disease<sup>38</sup> and obese young men<sup>131</sup>, respectively. Currently the non-disabled literature is unclear as to whether HIIT offers superior adaptations than MICT for lipid profiles<sup>39</sup><sup>132</sup>. However, over 24 weeks O'Donovan *et al*,<sup>133</sup> demonstrated high-intensity exercise was more effective in improving lipid profiles than MICT of equal energy cost. It is possible interventions of longer durations are required to determine the true-impact of exercise intensity on lipid profiles.

The two studies which have used time-matched training protocols in SCI demonstrated a decrease in fasting triglyceride concentrations (-19%<sup>42</sup> and -31%<sup>56</sup>) pre-post with vigorous-intensity exercise, but no change with moderate-intensity exercise training. Elevated fasting triglyceride concentrations have long been associated with CVD<sup>134, 135</sup>. Despite observing unremarkable concentrations of fasting triglycerides, participants with chronic paraplegia have shown exaggerated postprandial lipaemia<sup>136, 137</sup>. This exaggerated postprandial lipaemia is an important stimulus for the development of atherosclerosis<sup>138</sup>, and non-fasting triglyceride concentrations has revealed a stronger association with CVD than fasting<sup>139</sup>. As a result of a more sedentary lifestyle, reduced lipoprotein lipase slows postprandial triglyceride extraction from the systemic circulation and the atrophy of leg lean mass limits the ability to metabolise postprandial triglycerides as a fuel source<sup>140</sup>. To our knowledge, no studies have been conducted looking at the impact of upper-body exercise on postprandial lipaemia in persons with SCI. However, several studies have examined the effect of an acute bout of HIIT on the

400 postprandial triglyceride response to a high-fat mixed meal in able-bodied individuals.  
 401 These were summarised in a systematic review which concluded that an acute bout of  
 402 HIIT is similarly effective to MICT for reducing postprandial lipaemia <sup>141</sup>.

403

404

#### 405 **4 Cardiovascular Safety of HIIT**

406

407 Concerns have been raised over the safety of HIIT in populations at risk of  
 408 cardiometabolic disease and this should be specifically considered with reference to  
 409 SCI. Evidence from one recent non-disabled study, which included 5000 patients  
 410 undergoing supervised cardiovascular rehabilitation over a 7-year period, suggested that  
 411 the rate of adverse cardiovascular events was low with both HIIT and MICT, although  
 412 the event rate was higher with HIIT <sup>126</sup>. Specifically, the study reported an adverse  
 413 cardiovascular event rate of 1 per ~23,000 exercise hours during HIIT (2 non-fatal  
 414 cardiac arrests) compared with 1 per 129,000 exercise hours during MICT (1 fatal  
 415 cardiac arrest) <sup>126</sup>. However, various HIIT protocols have been used safely in patients  
 416 with post infarction heart failure <sup>142, 143</sup>, diastolic dysfunction <sup>144</sup>, coronary artery disease  
 417 <sup>145</sup> and atrial fibrillation <sup>146</sup>, while also improving clinical symptoms. A systematic  
 418 review of laboratory/hospital based exercise training studies in persons with SCI found  
 419 that adverse events were not common and those that occurred were not serious <sup>147</sup>. It  
 420 should be noted that the individuals in this review and within the studies mentioned  
 421 above were subject to extensive screening, and the cardiovascular safety of HIIT in this  
 422 population therefore requires further scientific appraisal. However, when appropriate  
 423 pre-participation screening is adopted the risks of adverse events are relatively low and  
 424 as previously suggested are '*likely comparable with the variant risks observed in the*  
 425 *general population*' <sup>148</sup>. SCI-specific special considerations for exercise, including the

management of autonomic dysreflexia, have been thoroughly addressed elsewhere<sup>15</sup>,  
<sup>149</sup>. It is noteworthy that patients with SCI are usually well-educated regarding the  
 symptoms and management of autonomic dysreflexia and there is no reason to speculate  
 that the occurrence of this will be increased with HIIT. As with any exercise  
 prescription, it would be recommended that individuals consult their clinician prior to  
 engaging in such exercise training programmes.

432

433

## 434 **5 Considerations for the application of HIIT to SCI populations**

435

Individuals with SCI  $\geq$  T6 exhibit a blunted cardiovascular response due to an absence  
 of cardiac sympathetic innervation<sup>150</sup> and a reduced catecholamine response during  
 exercise<sup>151</sup>. As a result of autonomic dysregulation, HR<sub>peak</sub> can be as low as 120 b/min.  
 Consequently in these individuals it would be difficult to prescribe an appropriate  
 exercise intensity using heart rate data. Evidence suggests that ratings of perceived  
 exertion (RPE)<sup>152</sup> and a talk test<sup>153</sup> can be effectively used to control exercise intensity  
 in persons with paraplegia. Consequently we advise an RPE  $\geq$ 16 and ‘speaking is not  
 comfortable’ as appropriate markers of ‘vigorous-intensity’ when performing upper-  
 body exercise.

445

The advantage of HIIT is that it enables deconditioned individuals to do a substantial  
 amount of work at a relatively high-intensity by incorporating rest periods, which  
 reduce local muscular fatigue. Fatigue following an acute 20 minute bout of HIIT in  
 patients with chronic fatigue syndrome was not clinically different to moderate-intensity  
 continuous exercise of a comparable workload<sup>154</sup>. Sensory impairment below the level

451 of injury can increase the risk of pressure sores when performing new activities for  
452 prolonged periods in the same position. Consequently as HIIT can be more time  
453 efficient and incorporates rest periods (ideal for performing regular pressure release)  
454 this could mitigate this risk and prevent skin breakdown.

455

456 Due to a reduced sweating capacity and inability to dilate superficial vasculature <sup>155</sup>,  
457 persons with higher-level injuries have an impaired heat loss during exercise <sup>156</sup>. While  
458 workload is increased with HIIT, possibly resulting in greater heat production, the total  
459 exercise time is less than MICT with recovery periods interspersed throughout.

460 Therefore we have no reason to believe that HIIT would impact core body temperature  
461 more than MICT. Still precautions should be taken when persons with SCI exercise in  
462 hot environments, as they have impaired thermoregulatory function <sup>157</sup>. Furthermore, to  
463 overcome blood pooling in lower extremities, associated with impaired venous return,  
464 an adequate cool down should be performed to prevent post-exercise hypotension.

465 Shoulder overuse injuries and musculoskeletal pain are also common in persons with  
466 SCI <sup>158, 159</sup>. While the higher workloads necessary to achieve vigorous-intensity might  
467 further contribute to these conditions, exercise has been proposed as a feasible,  
468 conservative, therapeutic treatment for shoulder pain in persons with SCI <sup>160</sup>.

469

470 Discussions regarding behaviour change and/or maintenance are outside the scope of  
471 this review. However, preliminary evidence would suggest that individuals with pre-  
472 diabetic conditions can adhere to HIIT over the short-term (4 weeks) and do so at a  
473 greater level than MICT <sup>123, 161</sup>. Questions have been raised regarding the adherence to  
474 HIIT over the long-term <sup>162, 163</sup> but we encourage researchers and practitioners to  
475 develop and evaluate strategies to incorporate HIIT into the everyday lives of persons

476 with SCI. We believe this is possible considering the evidence that non-disabled  
477 participants enjoyed HIIT more and were equally as confident to engage in HIIT as they  
478 were MICT<sup>164</sup>. Reassuringly, unpublished data has also demonstrated persons with SCI  
479 experienced greater enjoyment with HIIT and SIT protocols compared to MICT<sup>165</sup>.  
480 However, medical over protection may limit the prescription of vigorous-intensity  
481 exercise rehabilitation in this population. To help overcome this, the safety and efficacy  
482 of HIIT, particularly for persons with acute (<1 year) and higher level ( $\geq$ T6) SCI would  
483 need to be demonstrated by well-controlled longitudinal training studies. This is  
484 imperative when vigorous-intensity exercise has the potential to offer significantly  
485 greater improvements in certain cardiometabolic outcomes than MICT in a population  
486 at increased risk of chronic disease.

487

488

## 489 **6 Conclusions**

490

491 This special communication presents a case for the utility of HIIT as a strategy to  
492 promote vigorous-intensity physical activity and reduce cardiometabolic disease in  
493 persons with SCI. Data from SCI cohort studies, albeit collected using suboptimal  
494 research designs, seem to agree with consistent findings from studies in the general  
495 population that vigorous-intensity is superior to moderate-intensity exercise in  
496 improving a variety of cardiometabolic health outcomes. Importantly, these findings can  
497 be explained and supported by plausible physiological mechanisms. High-intensity  
498 virtual reality arm-exercise is already being investigated in persons with SCI<sup>166</sup> and the  
499 National Centre on Health, Physical Activity & Disability (NCHPAD) promote a  
500 selection of adapted vigorous-intensity exercise options (e.g. wheelchair burpees).

501 Increasing exercise-intensity could offer a simple, readily available, time-efficient  
502 solution to improve cardiometabolic health in persons with SCI. However, until stronger  
503 evidence has been collated concerning the safety and efficacy of HIIT in this population  
504 this is merely a call to action for researchers in the field and not necessarily an exercise  
505 guideline to be prescribed by clinicians.



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**Table 1** High-intensity interval training (HIIT) protocols used in non-disabled and SCI research studies.

**Table 2:** Description of exercise training studies that have compared the impact of exercise intensity on cardiometabolic health markers in persons with SCI.

**Figure 1:** Schematic of sprint-interval training (SIT), high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) protocols (Adapted from Gibala *et al*,<sup>51</sup> with permission).

**Figure 2:** Whole body Dual-energy X-ray absorptiometry (DEXA) scan of a female with neurological complete T7 injury sustained 6 years previously (a) and non-disabled female for comparative purposes (b). This figure visually highlights the drastic atrophy of lean mass and accumulation of intramuscular fat in the lower extremities of individuals with SCI.

**Table 1**

Authors	Exercise Intervals			Recovery Intervals		Total Session Time
	Number	Intensity	Duration	Intensity	Duration	
Little <i>et al.</i> , <sup>167</sup> N-D Harnish <i>et al.</i> , <sup>58</sup> SCI	10	90-110% Wmax ≥85% HRmax RPE ≥19	1-min	20-25% Wmax	1-2 min	~25 min
Tjønnna <i>et al.</i> , <sup>91</sup> N-D Sæter <sup>57</sup> † SCI	4	~85% Wmax 85-95% HRmax RPE ≥17	2.5-4 min	20-25% Wmax	3-5 min	~30 min
MacInnis <i>et al.</i> , <sup>37</sup> N-D Harnish <i>et al.</i> , <sup>58</sup> SCI	3	~70% Wmax 80-85% HRmax RPE ≥ 16	4-5 min	20-25% Wmax	3-5 min	~30 min

Table 1 Legend: *HRmax* maximum heart rate, *N-D* non-disabled, *RPE* ratings of perceived exertion, *SCI* spinal cord injury, *Wmax peak power output (Watts)*, *achieved during an incremental test to fatigue*

Suggested frequency for training interventions is 3 sessions/week. Low-intensity warm-up and extended cool-down are not included in the table, but should be incorporated into any applied protocol to optimise circulation and prevent post-exercise hypotension (Evans *et al.*,<sup>14</sup>). We have suggested appropriate RPE values so that these protocols can be followed in patients with blunted cardiovascular responses to exercise (spinal cord injury lesions ≥T6). There is scope for variation in the above HIIT protocols, as the frequency, intensity and the duration of the high-intensity intervals, as well as the characteristics and duration of the recovery periods, may all be manipulated to change the nature of the exercise stimulus and thus potentially the physiological adaptations associated with training<sup>168, 169</sup>

† Unpublished data

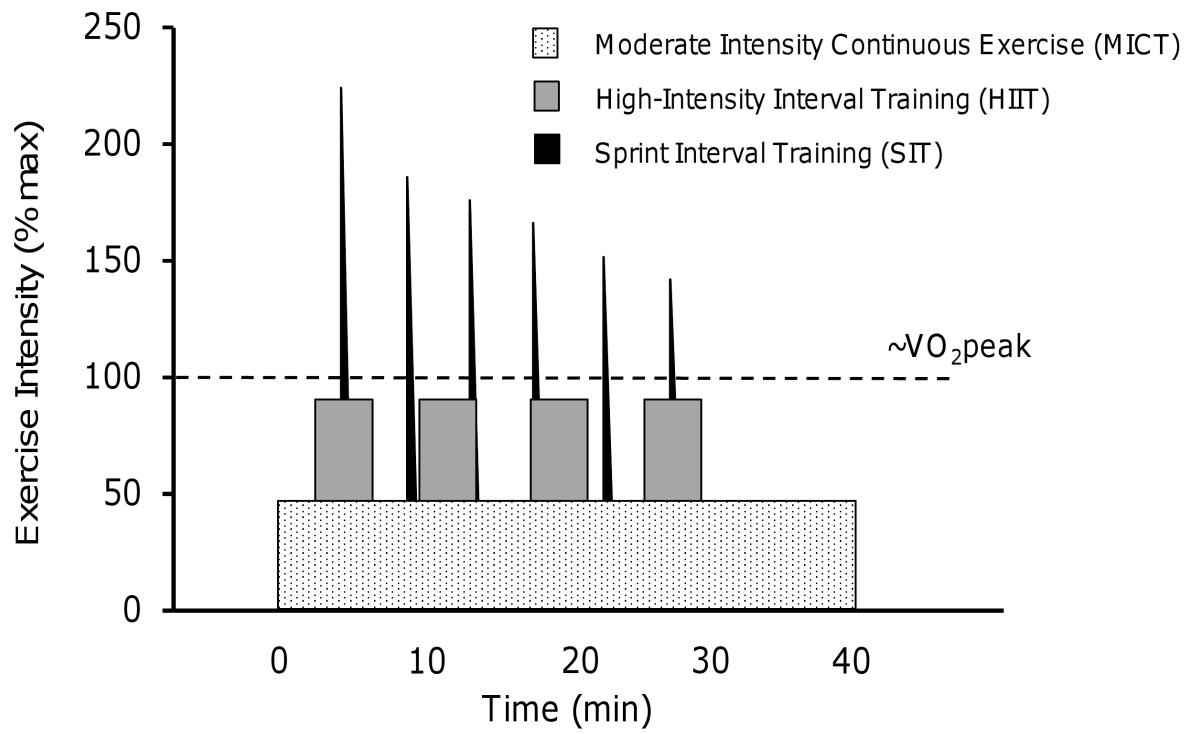
Table 2

Authors	Study Design	Participant Characteristics	Intervention	Outcome Measures		
				Change	No Change	
Hooker & Wells <sup>42 *</sup>	Pre-post parallel group WERG INT	6 (3F), 5 PARA, 1 TETRA, TSI; 4 mo - 19 yr Age; 26 - 36 yr	Frequency: 3 x wk Time: 20 min continuous Duration: 8 wks	Moderate-intensity (50 - 60% HRR)	↑ $\dot{V}O_2$ peak (10%), ↑ PPO (24%)	TC, TAG, LDL-C, HDL-C
		5 (2F), 3 PARA, 2 TETRA, TSI; 2 - 19 yr Age; 23 - 36 yr		High-intensity (70 - 80% HRR)	↑ $\dot{V}O_2$ peak (12%), ↑ PPO (13%) ↓ TAG (96 ± 28 to 78 ± 18 mg/dL; P ≤ 0.10), ↑ HDL-C (39 ± 11 to 47 ± 8 mg/dL; P ≤ 0.10), ↓ LDL-C (137 ± 26 to 116 ± 5 mg/dL; P ≤ 0.10)	TC
De groot <i>et al.</i> , <sup>56 *</sup>	Pre-post parallel group ACE INT	3 (2F), All PARA TSI; 61 - 225 days Age; 50 - 54 yr	Frequency: 3 x wk, Time: 60 min (3 & 2 minute work and rest intervals, respectively. Accumulated activity = 36 minutes) Duration: 8 wks	Moderate-intensity (40 - 50% HRR)	↑ $\dot{V}O_2$ peak (17%), ↑ PPO (24%)	TC, HDL-C, LDL-C, TAG. Non-significant improvement in IS (56%, measured via HOMA-CIGMA)
		3, 2 PARA, 1 TETRA TSI; 43 - 175 days Age; 20 - 38 yrs		High-intensity (70 - 80 % HRR)	↑ $\dot{V}O_2$ peak (50%), ↑ PPO (59%) ↓TAG (-31%), ↓ IS (-33%, measured via HOMA-CIGMA)	TC, HDL-C, LDL-C
Sæter <sup>57 †</sup>	Pre-post parallel group ACE INT	5, All PARA TSI; 15 ± 11 yrs Age; 43 ± 14 yrs	Frequency: 3 x wk Time: ~ 49 min (373 kcal) Duration: 8 wks Moderate-intensity: 70% peak HR			$\dot{V}O_2$ peak, PPO, TC, HDL-C, LDL-C, TAG, glucose
		5, All PARA (1F) TSI; 15 ± 14 yrs Age; 46 ± 6 yrs	Frequency: 3 x wk Time: 28 min (including 12 min active recovery) Duration: 8 wks High-intensity: 85 – 95% peak HR (4 x 4 min intervals)		↑ $\dot{V}O_2$ peak (9%, trend for an interaction effect between groups, P = 0.051), ↑ PPO (28%)	TC, HDL-C, LDL-C, TAG, glucose

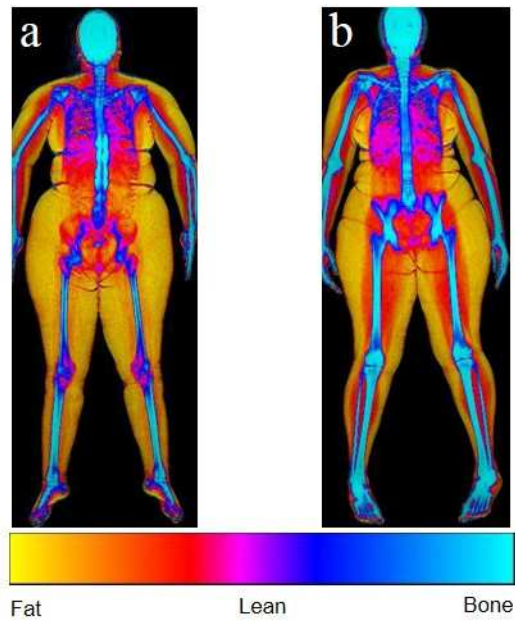
Table 1 Legend: *ACE* arm crank exercise, *HDL-C* high density lipoprotein cholesterol, *HR* heart rate, *HRR* heart rate reserve, *INT* intervention, *IS* insulin sensitivity, *LDL-C* low-density lipoprotein cholesterol, *PARA* paraplegic, *PPO* peak power output, *TAG* triglyceride, *TC* total cholesterol, *TETRA* tetraplegic, *TSI* time since injury,  $\dot{V}O_2 peak$  peak oxygen uptake, *WC* waist circumference, *WERG* wheelchair ergometry.

\* Note, authors refer to 70-80% HRR between studies as moderate<sup>42</sup> and high-intensity<sup>56</sup>, respectively. The terminology to describe exercise-intensity has been reclassified into moderate (40-60% HRR) and high-intensity (70-80% HRR).

† Unpublished data







## Warm Up (10 minutes)

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### Cardiovascular exercises (moving around independently in multi-directions)

- Marching with arm swings
- Walking backwards with knees straight
- Walking with leg curls
- Jogging
- Skipping
- Walking in slow motion (stepping with a one second pause before heel strike)
- Walking with longer strides
- Walking on heels
- Walking on toes

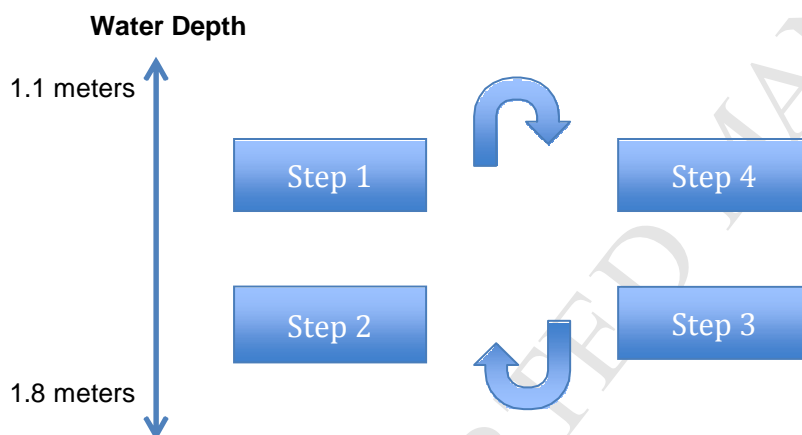
### Upper body stretches

- Cervical rotation and side flexion (2 reps x 10 second hold bilaterally)
- Shoulder raises (2 reps x 5 second hold)
- Shoulder rolls (10 reps bilaterally)

### Trunk stretches (with aqua noodle)

- Trunk rotation with arms abducted and externally rotated holding the aqua noodle (5 reps bilaterally)
- Arm raises reaching both arms overhead holding the noodle (5 reps bilaterally)
- Side bends pressing the aqua noodle into the water (5 reps x 5 second hold bilaterally)

## Gait re-education (20 minutes)



#### Activity

- Continuous walking
- Stepping up and down off the steps

#### Progression

- Increase walking speed
- Stepping over steps
- Change of direction (turning)
- Walking with fins (as tolerated)

## Strength exercises (10 minutes)

(2 minutes per exercise; 3 exercises selected per class with as many repetitions carried out as possible within the time)

### Circuits

- Sit to stand (using pool chair)
- Step ups (progression: raising arms up and down holding the aqua noodle)
- Side step ups
- Trunk rotation (performed standing back to back with a partner, passing ball x 10 reps bilaterally)
- Squats with aqua noodle
- Lunges

### Group

- Single leg stand (light finger hold at baseline progressed to 10 seconds with no hand support by session 12)
- Calf raises (10 reps at baseline progressed to 2 sets x 15 reps by session 12)
- Single leg calf raises (5 reps at baseline progressed to 15 reps by session 12)
- Push downs with aqua noodle (15 reps at baseline progressed to 30 reps by session 12)

## Cool Down (5 minutes)

(Performed standing by pool wall at water depth level T8 (8<sup>th</sup> thoracic vertebrae), 30 second hold x 3 reps)

- Quadriceps, hamstring and calf stretches performed using aqua noodle